Poster 345 Saturday

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Oritavancin Longitudinal *In Vitro* Activity Against Gram-positive Organisms from USA Medical Centers: Results from the SENTRY Antimicrobial Surveillance Program for 2010-2014 RE Mendes, RK Flamm, HS Sader, M Castanheira, DJ Farrell, RN Jones JMI Laboratories, North Liberty, IA, USA

Abstract

Background: Oritavancin is approved in the USA and European Union for the treatment of acute bacterial skin and skin structure infections caused by Gram-positive pathogens. This study evaluated oritavancin activity over time against Gram-positive isolates collected from USA hospitals in 2010-2014.

Methods: A total of 16,340 S. aureus, 1,313 coagulasenegative staphylococci (CoNS), 1,861 E. faecalis, 1,037 E. faecium. 2.505 beta-hemolytic streptococci (BHS) and 1.067 viridans group streptococci (VGS) were included. Bacteria were identified by standard algorithms and/or MALDI-TOF. Susceptibility testing was performed by CLSI methods; interpretation of MIC results used CLSI (2016) criteria.

Results: Oritavancin had MIC₅₀ and MIC₉₀ values of 0.03 and 0.06 µg/ml, respectively, against *S. aureus* (99.5 - 100.0%) susceptible), the methicillin-resistant (MRSA) subset (99.8 -100.0% susceptible) and CoNS during the study period. The only exception was noted in the 2011 sampling year that showed slightly higher MIC_{50} and MIC_{90} values ($MIC_{50/90}$, 0.06/0.12 µg/ml) against *S. aureus* and MRSA. Daptomycin $(MIC_{50/90}, 0.25/0.5 \,\mu$ g/ml), linezolid $(MIC_{50/90}, 1/1 \,\mu$ g/ml) and vancomycin (MIC_{50/90}, $1/1 \mu g/ml$) also had consistent MICs against S. aureus or MRSA over the study period. Similar $(\pm 1 \text{ doubling dilution})$ oritavancin MICs were obtained against E. faecalis and E. faecium over time. Ampicillin, daptomycin, linezolid and vancomycin showed consistent MIC₅₀ values (MIC_{50/90}, $1/1-2 \mu g/ml$) against *E. faecalis*, while daptomycin $(MIC_{50/90}, 2/2-4 \mu g/ml)$ and linezolid $(MIC_{50/90}, 1/1-2 \mu g/ml)$ had consistent MICs against *E. faecium* (80.1% VRE) over the period. VGS were highly susceptible to oritavancin (100.0%) with consistent MICs between 2010 and 2014. Similar MICs were obtained for oritavancin against BHS (99.1 - 99.8% susceptible) over the study period.

Conclusions: Oritavancin was highly active against an extensive longitudinal USA collection of clinically important Gram-positive pathogens. No significant year-to-year variations were noted in oritavancin activity against these clinical isolates.

Background

Oritavancin (ORBACTIV[®], oritavancin for injection) is approved by the Food and Drug Administration (FDA) and European Medicines Agency for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSIs). Potent *in vitro* oritavancin activity has been demonstrated against staphylococci, enterococci and streptococci. This activity originates from multiple mechanisms of action, including cellwall synthesis inhibition and perturbation of membrane barrier function, which provide oritavancin with rapid concentrationdependent bactericidal activity against *Staphylococcus aureus* and enterococci.

The *in vitro* activity of oritavancin was monitored during its development as part of the global SENTRY Antimicrobial Surveillance Program platform. The monitoring for antimicrobial activity and resistance has continued after regulatory approval as part of a postmarketing surveillance and risk management strategy framework. In this study, the *in vitro* activity of oritavancin was evaluated over time against Gram-positive clinical isolates collected from a network of USA hospitals located in nine Census regions during the surveillance program for 2010 - 2014.

Methods

Bacterial strain collection. A total of 16.340 S. aureus. 1,313 coagulase-negative staphylococci (CoNS), 1,861 Enterococcus faecalis, 1,037 Enterococcus faecium, 2,505 β-hemolytic streptococci (BHS) and 1,067 viridans group streptococci (VGS) were included. These isolates were submitted to the monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Program. Isolates were primarily identified by the participating laboratory and identification was confirmed by the reference monitoring laboratory (JMI Laboratories) by standard algorithms and supported by Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility test methods. Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document. Testing was performed using panels manufactured by Thermo Fisher Scientific (Oakwood Village, Ohio, USA). These panels provide oritavancin results equivalent to the CLSI-approved broth microdilution method supplemented with 0.002% polysorbate-80. Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event. Validation of the MIC values was performed by concurrent testing of CLSI-recommended quality control (QC) reference strains (S. aureus ATCC 29213, E. faecalis ATCC 29212 and Streptococcus pneumoniae ATCC 49619). All QC results were within published acceptable ranges (M100-S26). MIC interpretations were based on the CLSI (M100-S26) breakpoint criteria, as available.

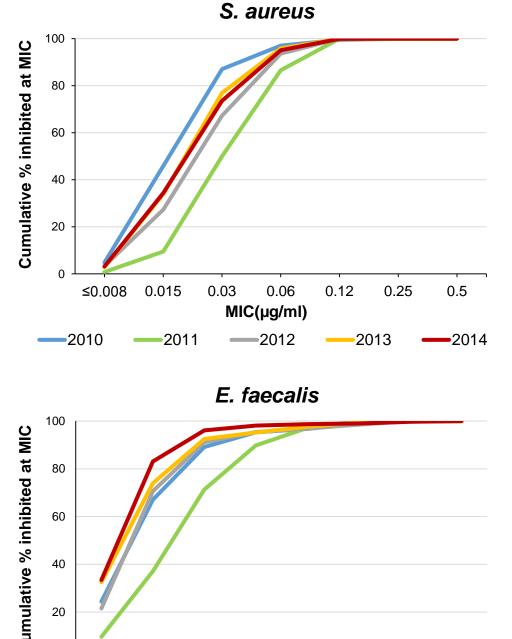
Results

- Oritavancin had MIC_{50} values of 0.03 µg/ml each year during 2010 through 2014 against *S. aureus* (Table 1), and against the entire *S. aureus* population (99.5 - 100.0% susceptible; **Table** 2). The oritavancin MIC distribution against S. aureus isolates of the 2011 sampling year was slightly different from those observed from 2010 and 2012-2014 (Table 1 and Figure 1).
- Daptomycin (MIC_{50/90}, 0.25/0.5 µg/ml), linezolid (MIC_{50/90}, 1/1 μ g/ml) and vancomycin (MIC_{50/90}, 1/1 μ g/ml) also had consistent MIC values against the S. aureus population over the study period. These agents were also highly active against the S. aureus isolates in this collection (99.8 - 100.0% susceptible; Table 2).
- The CoNS population showed similar yearly MIC distributions for oritavancin with consistent MIC₅₀ and MIC₉₀ results of 0.03 and 0.06 µg/ml (Table 1 and Figure 1). Equivalent oritavancin MIC_{50} and MIC_{90} results (0.03 and 0.06 µg/ml) were obtained year over year against the CoNS population (Table 2).
- The CoNS population (61.4% oxacillin-resistant) showed high resistance rates to most antimicrobial classes tested (15.6 -60.9% resistant to macrolides, lincosamides, fluoroquinolones, tetracyclines and folate pathway inhibitors; data not shown). Daptomycin (MIC_{50/90}, 0.25/0.5 µg/ml), vancomycin (MIC_{50/90}, $1/2 \mu g/ml$) and linezolid (MIC_{50/90}, 0.5/1 $\mu g/ml$) had high susceptibility rates (98.9 - 100.0% susceptible) against CoNS (**Table 2**).
- In general, oritavancin MIC₅₀ values were consistent year over year against *E. faecalis* (0.015 µg/ml; one value of 0.03 µg/ml in 2011) and *E. faecium* (0.03 μ g/ml) and the oritavancin MIC₉₀ for each species varied by no more than one doubling dilution (Table 1 and Figure 1).

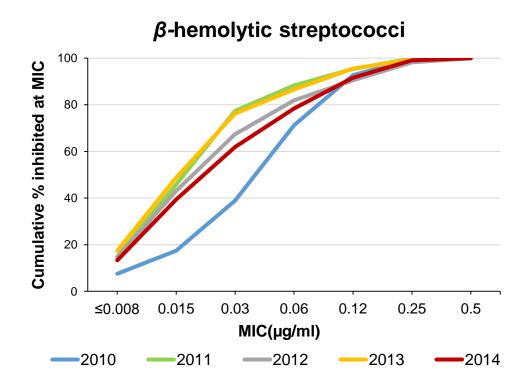
Results

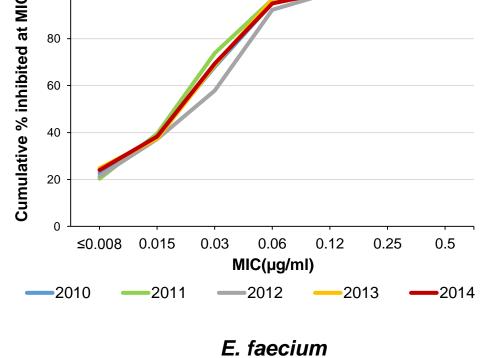
- Other comparator agents such as daptomycin (MIC₅₀, 1 μ g/ml; 100.0% susceptible), linezolid (MIC₅₀, 1 μ g/ml; ≥99.7% susceptible), vancomycin (MIC₅₀, 1 μ g/ml; ≥95.6% susceptible) and ampicillin (MIC₅₀, 1 μ g/ml; ≥99.7% susceptible) also showed consistent activity over time against *E. faecalis*, while daptomycin (MIC₅₀, 2 µg/ml; ≥98.9% susceptible) and linezolid (MIC₅₀, 1 μ g/ml; ≥97.8% susceptible) remained consistently active against *E. faecium* (Table 2).
- The yearly oritavancin MIC distributions against BHS were very similar, as they were for VGS (Table 1 and Figure 1), except for a single MIC₅₀ value observed against BHS in 2010, which was two-fold higher than those noted for the collections of 2011-2014.
- Daptomycin (MIC₅₀, 0.06-0.12 μ g/ml; 100.0% susceptible), linezolid (MIC₅₀, 0.5-1 μ g/ml; 100.0% susceptible), vancomycin (MIC₅₀, 0.25-0.5 μ g/ml; 100.0% susceptible), levofloxacin (MIC₅₀, 0.5 μ g/ml; ≥99.8% susceptible) and penicillin (MIC₅₀, 0.03-0.06 µg/ml; 100.0% susceptible) also showed consistently high activity over time against BHS.
- VGS were highly susceptible to oritavancin (100.0%) with consistent MIC results between 2010 and 2014, as was the case for other comparator agents (Table 2).

Figure 1: Oritavancin MIC distributions obtained against surveillance isolates. Data presented as the cumulative percentage of isolates inhibited at each MIC (µg/ml) per year.

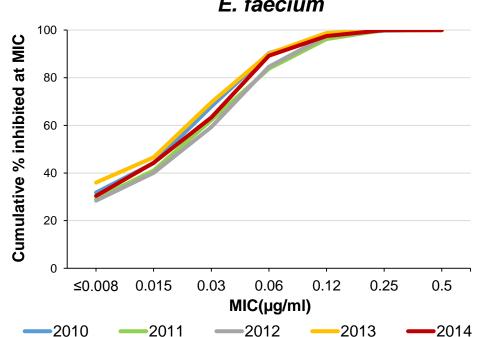


≤0.008 0.015 0.03 0.06 0.12 0.25 0.5 1 MIC(µg/ml) **—**2010 **—**2011 **—**2014





Coagulase-negative staphylococci



Viridans group streptococci

0.03 0.06

MIC(µg/ml)

0.12 0.25

<u> 2013 2014 </u>

≤0.008 0.015

—2010

—2011

Table 1. Antimicrobial activity and MIC distribution for oritavancin against contemporary (2010 – 2014) surveillance isolates.

Organism ^a	MIC (µ	ug/ml)	Ν	Number (cumulative %) inhibited at oritavancin MIC (μ g/mI) of:								
Year	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5			
S. aureus												
2010	0.03	0.06	156 (4.8)	1329 (45.9)	1332 (87.1)	326 (97.1)	78 (99.5)	15 (100.0)				
2011	0.03	0.12	24 (0.8)	265 (9.5)	1230 (50.0)	1114 (86.6)	406 (100.0)	. ,				
2012	0.03	0.06	98 (3.3)	892 (27.3)	1487 (67.3)	980 (93.7)	235 (100.0)					
2013	0.03	0.06	98 (2.9)	1100 (33.9)	1526 (76.9)	674 (95.9)	145 (>99.9)	0 (>99.9)	1 (100.0)			
2014	0.03	0.06	77 (3.1)	876 (34.4)	1100 (73.6)	600 (95.1)	136 (99.9)	2 (100.0)				
CoNS												
2010	0.03	0.06	61 (20.3)	58 (39.5)	103 (73.8)	69 (96.7)	9 (99.7)	1 (100.0)				
2011	0.03	0.06	39 (21.3)	29 (37.2)	38 (57.9)	63 (92.3)	13 (99.5)	1 (100.0)				
2012	0.03	0.06	63 (22.7)	49 (40.3)	72 (66.2)	79 (94.6)	15 (100.0)					
2013	0.03	0.06	53 (24.8)	27 (37.4)	67 (68.7)	60 (96.7)	7 (100.0)					
2014	0.03	0.06	81 (24.0)	48 (38.3)	105 (69.4)	86 (95.0)	17 (100.0)					
E. faecalis												
2010	0.015	0.06	134 (24.4)	235 (67.1)	121 (89.1)	34 (95.3)	8 (96.7)	12 (98.9)	5 (99.8)			
2011	0.03	0.06	33 (9.6)	94 (37.1)	117 (71.3)	63 (90.0)	25 (97.1)	10 (100.0)				
2012	0.015	0.03	70 (21.5)	160 (70.6)	67 (91.1)	14 (95.4)	5 (96.9)	5 (98.5)	5 (100.0)			
2013	0.015	0.03	109 (32.5)	139 (74.0)	62 (92.5)	9 (95.2)	8 (97.6)	6 (99.4)	2 (100.0)			
2014	0.015	0.03	103 (33.4)	153 (83.1)	40 (96.1)	6 (98.1)	2 (98.7)	1 (99.0)	2 (99.7)			
E. faecium												
2010	0.03	0.06	118 (31.8)	46 (44.2)	88 (67.9)	83 (90.3)	27 (97.6)	8 (99.7)	1 (100.0)			
2011	0.03	0.12	54 (29.2)	22 (41.1)	39 (62.2)	40 (83.8)	23 (96.2)	7 (100.0)				
2012	0.03	0.12	46 (28.4)	19 (40.1)	31 (59.3)	41 (84.6)	21 (97.5)	4 (100.0)				
2013	0.03	0.06	58 (36.0)	17 (46.6)	37 (69.6)	33 (90.1)	14 (98.8)	2 (100.0)				
2014	0.03	0.12	48 (30.4)	22 (44.3)	30 (63.3)	41 (89.2)	13 (97.5)	4 (100.0)				
BHS												
2010	0.06	0.12	38 (7.5)	50 (17.4)	109 (38.9)	164 (71.2)	109 (92.7)	35 (99.6)	2 (100.0)			
2011	0.03	0.12	71 (14.9)	148 (45.8)	151 (77.4)	52 (88.3)	34 (95.4)	21 (99.8)	1 (100.0)			
2012	0.03	0.12	52 (14.5)	144 (43.1)	122 (67.4)	73 (81.9)	43 (90.5)	39 (98.2)	9 (100.0)			
2013	0.03	0.12	81 (17.4)	152 (48.8)	133 (76.2)	50 (86.6)	43 (95.5)	19 (99.4)	3 (100.0)			
2014	0.03	0.12	62 (13.3)	139 (39.4)	120 (61.9)	88 (78.4)	70 (91.6)	40 (99.1)	5 (100.0)			
VGS												
2010	≤0.008	0.06	100 (61.0)	25 (76.2)	16 (86.0)	15 (95.1)	8 (100.0)					
2011	≤0.008	0.06	103 (52.8)	29 (67.7)	22 (79.0)	24 (91.3)	14 (98.5)	3 (100.0)				
2012	≤0.008	0.06	167 (65.0)	35 (78.6)	22 (87.2)	24 (96.5)	9 (100.0)					
2013	≤0.008	0.06	113 (57.1)	40 (77.3)	24 (89.4)	13 (96.0)	7 (99.5)	1 (100.0)				
2014	≤0.008	0.06	144 (56.9)	39 (72.3)	32 (85.0)	23 (94.1)	15 (100.0)					

Table 2. Antimicrobial activity of oritavancin and comparator agents against surveillance isolates (2010 – 2014).

MIC ₅₀ /MIC ₉₀ and % susceptible by year: ^a												
Organism ^a	2010		2011		2012		2013		2014		Overall	
S. aureus												
Oritavancin	0.03/0.06	99.5	0.03/0.12	100.0	0.03/0.6	100.0	0.03/0.06	>99.9	0.03/0.06	99.9	0.03/0.06	99.9
Daptomycin	0.25/0.5	>99.9	0.25/0.5	99.9	0.25/0.5	>99.9	0.25/0.5	99.9	0.25/0.5	99.8	0.25/0.5	99.9
Vancomycin	1/1	100.0	1/1	100.0	1/1	100.0	1/1	100.0	1/1	100.0	1/1	100.0
Linezolid	1/1	100.0	1/2	>99.9	1/1	>99.9	1/1	99.9	1/1	>99.9	1/1	>99.9
TMP-SMX	≤0.5/≤0.5	98.5	≤0.5/≤0.5	98.6	≤0.5/≤0.5	98.6	≤0.5/≤0.5	98.7	≤0.5/≤0.5	98.2	≤0.5/≤0.5	98.5
CoNS												
Oritavancin	0.03/0.06	-	0.03/0.06	-	0.03/0.06	-	0.03/0.06	-	0.03/0.06	-	0.03/0.06	-
Daptomycin	0.25/0.5	100.0	0.25/0.5	100.0	0.5/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0
Vancomycin	2/2	100.0	1/2	100.0	1/2	100.0	1/2	100.0	1/2	100.0	1/2	100.0
Linezolid	0.5/1	99.9	0.5/1	100.0	0.5/1	98.9	0.5/1	99.5	0.5/0.5	99.4	0.5/1	99.3
E. faecalis												
Oritavancin	0.015/0.06	96.7	0.3/0.12	97.1	0.015/0.03	96.9	0.015/0.03	97.6	0.015/0.03	98.7	0.015/0.06	97.4
Daptomycin	1/1	100.0	1/2	100.0	1/2	100.0	1/1	100.0	1/2	100.0	1/2	100.0
Vancomycin	1/2	95.6	1/2	97.4	1/2	95.7	1/2	96.4	1/2	98.1	1/2	96.5
Ampicillin	1/2	100.0	1/2	100.0	1/2	99.7	1/2	100.0	1/1	100.0	1/2	99.9
Linezolid	1/2	99.8	1/1	100.0	1/2	100.0	1/1	100.0	1/1	99.7	1/1	99.9
E. faecium												
Oritavancin	0.03/0.06	-	0.03/0.12	-	0.03/0.12	-	0.03/0.06	-	0.03/0.12	-	0.03/0.12	-
Daptomycin	2/2	99.7	2/4	98.9	2/2	100.0	2/2	100.0	2/2	100.0	2/2	99.7
Vancomycin	>16/>16	19.9	>16/>16	23.2	>16/>16	24.7	>16/>16	26.7	>16/>16	25.9	>16/>16	23.2
Linezolid	1/2	97.8	1/1	99.5	1/2	100.0	1/1	99.4	1/1	98.7	1/1	98.8
BHS												
Oritavancin	0.06/0.12	99.6	0.03/0.12	99.8	0.03/0.12	98.2	0.03/0.12	99.4	0.03/0.12	99.1	0.03/0.12	99.2
Daptomycin	0.06/0.25	100.0	0.06/0.25	100.0	0.12/0.25	100.0	0.12/0.25	100.0	0.12/0.25	100.0	0.12/0.25	100.0
Vancomycin	0.5/0.5	100.0	0.5/0.5	100.0	0.5/0.5	100.0	0.5/0.5	100.0	0.25/0.5	100.0	0.5/0.5	100.0
Penicillin	0.03/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0
Linezolid	1/1	100.0	1/1	100.0	1/1	100.0	1/1	100.0	0.5/1	100.0	1/1	100.0
Levofloxacin	0.5/1	99.6	0.5/1	99.0	0.5/1	98.8	0.5/1	99.4	0.5/1	99.6	0.5/1	99.3
VGS												
Oritavancin	≤0.008/0.06	100.0	≤0.008/0.06	100.0	≤0.008/0.06	100.0	≤0.008/0.06	100.0	≤0.008/0.06	100.0	≤0.008/0.06	100.0
Daptomycin	0.25/0.5	100.0	0.25/1	100.0	0.25/1	100.0	0.25/1	100.0	0.25/0.5	100.0	0.25/1	100.0
Vancomycin	0.5/0.5	100.0	0.5/1	100.0	0.5/1	100.0	0.5/0.5	100.0	0.5/0.5	100.0	0.5/1	100.0
Penicillin	0.06/1	69.5	0.06/0.5	75.4	0.06/1	73.9	0.06/0.5	80.4	0.06/0.5	79.4	0.06/0.5	100.0
Linezolid	1/1	100.0	1/1	100.0	1/1	100.0	0.5/1	99.5	0.5/1	100.0	0.5/1	>99.9
Levofloxacin	1/2	91.5	1/2	91.8	1/2	93.8	1/2	93.8	1/2	94.5	1/2	93.2
a. TMP-SMX = trimet												

a. TMP-SMX = trimethoprim-sulfamethoxazole; CoNS = coagulase-negative staphylococci; BHS=β-hemolytic streptococci; VGS=viridans group streptococci. b. Breakpoint criteria for comparators according to the CLSI M100 document (2016). Oritavancin breakpoints as follows: S. aureus at ≤0.12 µg/ml for susceptible; vancomycin-susceptible E. faecalis at ≤0.12 µg/ml for susceptible was applied for the E. faecalis population (3.5% VRE); S. agalactiae, S. pyogenes and S. dysgalactiae at ≤0.25 µg/ml for susceptible applied for BHS; S. anginosus group at ≤0.25 μg/ml for susceptible applied for VGS. "-" = breakpoint not available.

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Conclusions

- isolates.
- streptococci.

Disclosures

References

- Informational Supplement. Wayne, PA, USA.

- characteristics (Annex I). Available at November 2015.
- Chemother 70: 1625-1629.
- November 2015.

• Oritavancin inhibited 99.9% (17,633/17,653) of all staphylococci, 97.4% (2,824/2,898) of all enterococci and 99.4% (3,552/3,572) of all streptococci at the S. aureus ($\leq 0.12 \mu g/ml$), vancomycin-susceptible *E. faecalis* (≤ 0.12 μ g/ml) and streptococcal (≤0.25 μ g/ml) breakpoints, respectively. Moreover, no significant year-to-year variations were noted in oritavancin activity against these clinical

 Other comparator agents such as daptomycin and linezolid also demonstrated consistent in vitro activity over time against all species or group of species. Vancomycin was consistently active against staphylococci, *E. faecalis* and streptococci, and levofloxacin was active against

• This study also reports on the MDR nature of CoNS and E. *faecium* species, against which only a limited number of agents show antimicrobial activity. In contrast, sustained in vitro activity of penicillins was observed over time against E. faecalis and BHS clinical isolates from USA hospitals.

• This study was sponsored by an educational/research grant from the Medicines Company (Parsippany, New Jersey, United States) via the SENTRY Antimicrobial Surveillance Program platform.

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